Death in amphetamine users: causes and rates*

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Summary: The world medical literature contains 43 reports of deaths associated with amphetamines in a 35-year period. These included seven cerebrovascular accidents, six sudden cardiac deaths, three cases of hyperpyrexia, eight poisonings of uncertain mechanism and seven cases of medical complications of intravenous injection; the remainder were of uncertain cause. In contrast, in Ontario alone, in 1972 and 1973 there were 26 deaths in amphetamine users, of which 16 were due to accident, suicide or homicide. Of the remaining cases, two were cardiac, two hepatic and the rest were mixed drug overdose. Pulmonary granulomata, subacute hepatitis and other lesions resulting from intravenous drug use were common findings at autopsy. On the basis of the estimated number of regular users of intravenous amphetamine in Ontario, the mortality rate in such users is at least four times as high as in the general population of the same age, and is comparable to that in alcoholics and heroin addicts. However, the absolute number of alcohol-related deaths is far greater than the number of deaths in amphetamine or heroin users.

Résumé: *Les décès parmi les usagers d'amphétamine: les causes et les taux*

On trouve dans la littérature mondiale 43 rapports de décès constatés chez les usagers d'amphétamines, couvrant une période de 35 ans. Parmi ces cas figurent sept accidents cérébrovasculaires, six morts subites par cardiopathie, trois cas d'hyperpyrexie, huit cas d'intoxication dont le mécanisme reste obscur et sept cas de complications médicales relevant d'injections intraveineuses. La cause des autres décès demeure incertaine. Par contre, en Ontario seulement, durant les seules années 1972 et 1973, on comptait 26 décès chez des habitués de l'amphétamine, dont 16 étaient attribuables à l'accident, au suicide ou à l'homicide. Parmi les cas restants on notait deux cardiaques et deux hépatiques, les autres étant des cas mixtes de surdosage. A l'autopsie on découvrait fréquemment des granulomatomes pulmonaires, de l'hépatite subaiguë et d'autres lésions résultant de l'emploi de médicaments intraveineux. Si on se base sur le nombre estimé des usagers réguliers d'amphétamine par voie IV, on admet que la mortalité dans ce groupe est au moins quatre fois plus élevée qu'au sein de l'ensemble de la population d'âge égal et est comparable à celle qui existe chez les alcooliques et les héroïnomanes. Il faut cependant reconnaître que le nombre absolu des décès chez les alcooliques est de très loin supérieur à celui constaté chez les habitués d'amphétamine ou d'héroïne.

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During the decades in which the amphetamines were used primarily for medical purposes, these drugs were considered remarkably safe and only rarely responsible for death. With the advent of widespread nonmedical use, especially the intravenous use of illicit methamphetamine ("speed"), this view was replaced by alarming claims of high mortality risk. Now that the speed "epidemic" has apparently subsided, the view that there is little mortality attributable to the drug, especially in relation to the direct effect of overdoses, is again being advanced.

Yet these changes of opinion have not been based on thoroughly documented evidence. A survey of the medical literature up to 1963[1] yielded only nine reported cases of death attributed to amphetamine toxicity. The same nine cases were found in an independent survey 3 years later.[2] Since then no systematic survey of the literature appears to have been conducted until 1974.[3] The present paper is based on a detailed examination of the fatalities that have been reported, and on a comparison with available medicolegal data from the Province of Ontario, which permits some inferences about the nature and frequency of amphetamine-related deaths; the paper also indicates the type of investigation that will be needed for reliable answers.

Amphetamines are understood here to include racemic (*d,l*) amphetamine, *d*-amphetamine, methamphetamine, phenmetrazine hydrochloride, methylphenidate hydrochloride, diethylpropion hydrochloride and propylhexedrine, the ring-saturated analog of methamphetamine. All these drugs have in common roughly the same group of sympathomimetic, central stimulant and anorexiant effects that underlie both their medical and nonmedical uses. Hallucinogenic derivatives of amphetamine, such as mescaline, methylenedioxyamphetamine (MDA) and *p*-methoxyamphetamine (PMA), are not included because their actions have led to a different pattern of nonmedical use, and they have never had any recognized medical application.

Review of published case reports

The world literature includes 43 reported cases of death associated in some way with amphetamines. The causes of death fall into two major categories: those directly attributable to the pharmacologic actions of the drugs and those attributable to secondary complications related to the route of administration. In some instances, examination of the evidence provided has led us to a different conclusion from that of those authors as to the cause or mechanism of death. The following discussion is based on our own conclusions concerning those cases.

Deaths directly attributable to amphetamine action

The amphetamines are generally considered to act through

*A more detailed presentation of the data on which this paper is based will appear in "Research Advances in Alcohol and Drug Problems" (New York, Wiley), tentatively vol. 3.

a combination of displacement of stored transmitter substances from catecholaminergic nerve endings, direct postsynaptic adrenergic action and varying degrees of monoamine oxidase (MAO) inhibitor activity. Therefore, one can expect the mechanisms of death to be typical of excessive catecholamine activity. This is borne out by the following case histories.

Cerebrovascular hemorrhage: This group contains seven clear-cut cases of death due to intracranial hemorrhage.[4-10] The diagnosis was proved at autopsy in all but one case,[10] in which the clinical picture left little room for doubt. It is reasonable to attribute hemorrhage in these cases to acute hypertensive crisis because this would be expected from catecholamine overdose and because elevated blood pressure was specifically mentioned in three case reports.[7-9] Three patients were in an age group in which vascular degenerative changes could have been an important factor in the rupture of the vessel. In fact, cerebral atheroma was specifically mentioned in one instance.[9] However, three patients were less than 30 years of age, and in the reports concerning two of them the absence of vascular abnormality was emphasized.

Four of the seven cases illustrate the now well recognized danger of combining amphetamines with MAO inhibitors such as tranylcypromine sulfate and phenelzine sulfate. The inhibition of monoamine oxidase leads to a much greater discharge of catecholamine in response to even a small dose of amphetamine. Three patients[5, 9, 10] received the combination from their physician before this hazard was generally recognized. One patient[8] took *d*-amphetamine on her own initiative during treatment with phenelzine. In the remaining three patients the hemorrhage appears to have resulted from the action of amphetamine or methamphetamine alone, but in much larger doses than were taken in combination with the MAO inhibitors. An additional case report[11] should probably be considered here, although the history cannot be regarded as clear-cut. Although the patient had been a known heavy user of *d*-amphetamine, she was given tranylcypromine by her physician. After she had taken eight times the prescribed dose, a fatal intracranial hemorrhage occurred. It is not clear whether she actually took amphetamine concurrently, but this cannot be ruled out because of her history of addiction.

Acute cardiac failure: One of the known effects of catecholamines is sensitization of the myocardium to ectopic stimuli, increasing the risk of ventricular arrhythmias. Indeed, part of the antiarrhythmic effect of propranolol is based on its β-blocking action. It is of interest, therefore, that six patients died suddenly with electrocardiographic,[12, 13] pathologic[14] or circumstantial[15-17] evidence of ventricular fibrillation. Another[16] died of acute cardiac failure superimposed on chronic cor pulmonale. Two individuals[18, 19] were found dead, but the pathologic findings suggested acute left ventricular failure, even though the authors did not specify the cause of death.

As with cerebrovascular hemorrhage, other factors may have contributed to death. In one case[12] the amphetamine was administered with nikethamide, caffeine and sodium benzoate; these drugs can contribute to myocardial hyperirritability. In another case[13] the patient also received large doses of thyroxine and digitalis, and had hypokalemia due to overzealous administration of trichlormethiazide, all of which would be expected to increase the risk of ventricular fibrillation. In two cases[14, 17] pathologic examination revealed scattered myocardial lesions that might have served as ectopic foci under the influence of the amphetamine. All but two of these patients were aged 25 years or less, and none had evidence of rheumatic fever or other illness severe enough to explain the sudden deaths.

Hyperthermia: In three cases[1, 20, 21] death was clearly associated with hyperpyrexia (temperatures of the order of 43°C). In one case[1] the immediate cause of death was ventricular fibrillation, but this was probably due to hyperthermia rather than to a direct effect of amphetamine on the myocardium. Neither the clinical nor the pathologic findings provided any recognizable cause of hyperthermia other than the drug. Because of the importance of catecholamines in central thermoregulatory processes, it is reasonable to attribute the disturbance to a direct pharmacologic effect of the amphetamines. This suggestion[1, 21] is strengthened by recent accounts of hyperthermia associated with death occurring after overdose of PMA.[22] An examination of the pharmacologic mechanism operant in these cases is being prepared by Sellers and Robinson.[23]

In three other cases[19, 24, 25] the highest recorded temperature (41°C) would not ordinarily be expected to lead to a fatal outcome. However, the other clinical features suggest that the temperature may well have been higher at other times during the fatal illness.

Mechanism of death uncertain: In eight patients there appears to be a definite connection between the intake of amphetamines and death, but the mechanism is unclear.

Two of these patients were small children who swallowed large amounts of *d*-amphetamine[26] and methylphenidate plus tripelennamine.[27] In both, autopsy showed severe cerebral congestion and edema, and in one[26] there was internal hydrocephalus and brain stem compression. In the other the edema may have been secondary to repeated tonic-clonic convulsions shortly before death, in which the tripelennamine may have been an important factor.

In five cases[17-19, 28, 29] virtually no history was available and the pathologic findings were not sufficiently specific to permit assignment to any of the groups discussed above. In one further case[17] death was attributed to septicemia resulting from unsterile parenteral administration, but the history and pathologic findings do not support such a claim.

Deaths due to complications of intravenous administration

It is now accepted that intravenous self-administration of drugs for nonmedical purposes is often done with unsterile equipment and bad technique. Consequently, there have been many reports of morbidity due to viral hepatitis, septicemia, foreign body reactions and other pathologic processes not related to the specific pharmacologic actions of the drugs.

The present series includes one death from subacute bacterial endocarditis,[29, 30] one from septicemia with acute bacterial endocarditis,[31] one from cor pulmonale due to foreign body granulomata in the lungs with consequent pulmonary hypertension,[32] and four associated with necrotizing angiitis.[33, 34] Foreign body granulomata in the lungs at autopsy were also reported in two cases,[16, 29] but the histories do not permit any decision as to whether the sudden deaths were related to this finding. Of the four patients with necrotizing angiitis, three died of renal failure and one of cerebral hemorrhage. The last patient is not considered to have had cerebrovascular hemorrhage attributable to amphetamine because she died in hospital after a long illness, during which she presumably had no further access to the drug.

When necrotizing angiitis was first described as a complication of intravenous drug use, methamphetamine was suggested as the common causal factor.[33] No cases have been reported in those using amphetamines exclusively by the oral route, so the importance of the intravenous route must be emphasized. Koff, Widrich and Robbins[34] have recently suggested that the disease may be due to hepatitis B virus rather than to the drug. One patient, who died of necrotizing angiitis with renal failure and pancreatitis, is not really known to have taken methamphetamine at all. She was included in the original series[33] in which methamphetamine was suggested as the common etiologic factor, but the case

record describes her only as having "a history of drug abuse". This issue requires further investigation.

Deaths of uncertain cause

In four cases an etiologic role was attributed to amphetamine, but there is reason to doubt the connection. The first case was that of a 1-year-old child who swallowed large amounts of amphetamine and ferrous sulfate tablets.[35] Although the authors ascribed primary importance to the amphetamine, the description of the clinical course and the pathologic findings are quite compatible with those of acute iron poisoning.

The second patient, a known alcoholic, died in hepatic failure,[36] which could well be attributed to alcoholic hepatitis alone. He took a large amount of amphetamine (together with a large amount of alcohol), to which the authors ascribed a contributory role. However, there is no independent evidence of amphetamine hepatotoxicity that would lend credence to this suggestion.

The third patient[37] was a young woman who died of pancytopenia attributed to toxic depression of the bone marrow. She was a regular heavy user of *d*-amphetamine, continuing even while in hospital. Since this is the only case of its kind ever reported, despite the wide use of amphetamines, the possible role of other toxic factors must be considered. She apparently used barbiturates also and the possible use of other drugs cannot be ruled out.

The fourth case[38] was that of a regular user of amphetamine who died of acute myeloblastic leukemia. Present views on the etiology of leukemias do not lend support to any causal role of amphetamine in this case. Prior use of *d*-amphetamine was recently reported to be associated with a significantly increased risk of Hodgkin's disease,[39] although this association has since been challenged.[40]

Comment

Despite the widespread medical use of amphetamines in the past, remarkably few fatalities have been reported in patients taking the drugs under supervision. Only five such cases have been described, and three of these involved the simultaneous administration of MAO inhibitors. Most of the reported deaths occurred in people using the drugs nonmedically or without the knowledge of their physicians. However, among persons for whom the history permits a reasonable conclusion, nearly half (13 patients) could not be considered regular users or "addicts", and all of them died of a single overdose. In contrast, among the 15 known regular users who died, 9 died from complications of intravenous use and only 6 died from an overdose, in 2 of whom the simultaneous use of MAO inhibitors was the main factor leading to death.

Amphetamine-related deaths in Ontario in 1972 and 1973

The cases reported in the world literature cover a span of 35 years and have been gathered from a number of different countries and different types of populations. It is therefore of interest to see how the pattern of death reflected in them corresponds to that occurring within a single population that includes substantial numbers of amphetamine users. For this purpose the records of the chief coroner of the Province of Ontario for 1972 and 1973 were searched for all deaths in which amphetamines were involved in any way; Table I summarizes the main features in 26 cases gathered from this source. The first 14 deaths occurred during 1972 and the remainder during 1973. During the same period there were about 60 000 deaths a year from all causes in Ontario, of which about 40% were reviewed by coroners. The criteria for coroners' examinations are such that most drug-related deaths are likely to be investigated.

The pattern of causes of death in this series is strikingly different from that revealed in the literature survey. The most distinct difference is that two thirds of the deaths were of a violent nature: seven were due to accidental violence, seven to suicide and three to homicide. In one accidental death (case 4) and three suicides (cases 3, 11 and 20) there may be insufficient evidence to connect

Table I—Deaths in amphetamine users in Ontario in 1972 and 1973

Case no.	Sex	Age	Drug*	Route of administration	Regular user	Other drugs used	Cause of death
1	M	44	Meth-A	IV	Yes	—	Homicide
2	M	25	Meth-A	IV	Yes	Salicylate	Homicide
3	F	18	Meth-A	Oral	?	—	Jumped from bridge (suicide)
4	M	35	Meth-A	IV	Yes	—	CO poisoning
5	F	18	Meth-A	IV	Yes	LSD, mescaline	Hepatitis with massive hepatic necrosis
6	M	25	Meth-A	IV	Yes	—	Hepatitis, posthepatitic cirrhosis, massive GI hemorrhage
7	F	55	d-A	Oral	Yes	Meth-A, barbiturate	Left ventricular failure
8	M	28	Meth-A	IV	Yes	—	CO poisoning
9	M	24	Meth-A	IV	?	Barbiturate	Accidental fall
10	M	26	Meth-A	?	Yes	MDA, alcohol	Asphyxia by aspiration of vomitus
11	F	41	A	Oral	Yes	Barbiturate, primidone, salicylate	Overdose (suicide)
12	M	22	Meth-A	?	?	Alcohol	Slashed wrists (suicide)
13	F	26	Meth-A	IV	Yes	Barbiturates, diazepam	Overdose
14	M	26	Meth-A	IV	Yes	Alcohol	Hit by car
15	F	40	d-A	Oral	Yes	Alcohol, prescription drugs	Left ventricular failure
16	M	19	Meth-A	?	Yes	—	Gun shot (suicide)
17	M	22	Meth-A	IV	Yes	Barbiturates	Gun shot (suicide)
18	M	25	Meth-A	IV	Yes	Barbiturates	Gun shot (suicide)
19	M	18	Meth-A	IV	Yes	Alcohol	Asphyxia by aspiration of vomitus
20	M	22	A	?	No	—	Gun shot (suicide)
21	M	18	Meth-A	IV	Yes	Salicylate, propoxyphene	Freezing after accidental fall
22	M	19	Meth-A	IV	Yes	Alcohol	Automobile accident
23	M	24	Meth-A	IV	Yes	Methaqualone, diphenhydramine	Asphyxia by aspiration of vomitus
24	F	22	Meth-A	IV	Yes	Alcohol, methadone	Overdose
25	M	27	Meth-A	?	Yes	Barbiturates	Accidental homicide
26	M	23	Meth-A	?	Yes	—	Drowning

*Abbreviations: A, amphetamine; d-A, dextroamphetamine; meth-A, methamphetamine.

the amphetamines with the behaviour leading to death, and in case 22 the major factor may have been the high blood alcohol concentration. In the remaining 12 cases, however, the behaviour leading to death is wholly consistent with amphetamine intoxication and with the toxicologic evidence. Erratic behaviour, paranoid ideas, overt aggression, feelings of omnipotence, and in some cases confusion are all well documented manifestations of amphetamine intoxication.[2] Many of these features are illustrated in the following case histories.

Case 14

A 26-year-old man, well known to the police as a speed user, had been drinking beer and using speed most of the day. He was known to go "mentally blank" when "coming down" from the effects of speed. In this condition he wandered onto a major highway late at night with his back to the traffic, and was struck and killed by a car. Toxicologic examination confirmed the presence of alcohol, amphetamine and methamphetamine in the body.

Case 17

A 22-year-old man was a known "speed freak" who became paranoid about police whenever he got "high". He shot and killed a police officer while under the influence of the drug. He was traced by the police to a house, which was then surrounded. He refused to surrender and shot himself in the head. Incidental findings at autopsy included numerous sclerosed veins in the forearms, multiple foreign-body granulomata in the lungs, and foci of chronic inflammatory cells in the portal areas. Toxicologic examination revealed the presence of amphetamine, methamphetamine and barbiturates in the body.

Depression is both a symptom of amphetamine withdrawal and a cause of amphetamine use. Suicide among amphetamine users is therefore not surprising. A further possibility is that amphetamines, when taken by depressed persons, may mobilize them sufficiently to enable them to commit suicide; cases 3 and 20 may belong in this category.

The remaining nine deaths are attributable to medical causes. Two appeared to be cardiac deaths resulting directly from drug toxicity. The details of one such case are summarized as follows:

Case 15

A 40-year-old woman was found dead in bed, with a large amount of prescription drugs by her bedside, including two preparations containing *d*-amphetamine. The lungs were intensely congested, yet the myocardium and coronary vessels were normal, as was the heart size. The blood contained amphetamine and ethanol. Death was attributed to acute cardiac failure due to the drug combination.

Two deaths resulted from viral hepatitis or posthepatitic cirrhosis and clearly belong in the category of complications of intravenous administration. Surprisingly, reports of hepatitis were not found in the literature despite the many references to the frequency of its occurrence among intravenous drug users.[41] The remaining five cases may be classed as being cases of drug overdose (though not necessarily overdose of amphetamines); three resulted from asphyxia of vomitus, and two by unknown mechanisms.

Another important feature is the frequency of multiple drug use. This should come as no surprise because few long-term amphetamine users are not also multiple drug users. The classification of users by single drugs is rather arbitrary. In 18 of the 26 cases the history or toxicologic examination indicated the use of other drugs in addition to the amphetamines. Indeed, in nine cases other drugs or toxic materials were present in the body in such large amounts that they were probably primarily responsible for the death. These drugs or chemicals included carbon monoxide (cases 4 and 8), MDA (case 10), alcohol (cases 15, 19 and 22), methaqualone (case 23) and barbiturates and minor tranquillizers (cases 11 and 13). However, even in these cases it is not possible to exclude some contribution of the amphetamines to the fatal outcome. For example, in case 8 the death was due to carbon monoxide poisoning, but this resulted from behaviour that was most probably provoked by the amphetamine. In case 15 the blood alcohol concentration alone was too low to have caused death, but the addition of amphetamine might well have contributed to a ventricular arrhythmia. In case 19 the testimony of the witnesses related the death almost immediately to the injection of speed, even though the main drug found on toxicologic examination was alcohol. The motor vehicle accident in case 22 could be attributed to the alcohol alone, yet the amphetamine probably contributed to the reckless and overconfident behaviour.

The absence from the medical literature of any description of violent deaths in amphetamine users is perhaps not surprising. Such cases, if reported at all, are more likely to be found in the popular press or the legal or criminologic literature. Rather, it is more surprising that the psychiatric literature does not appear to contain any documented reports of suicides during the amphetamine withdrawal depression. The lack of clinical reports of deaths from hepatitis may in a sense be an artefact, such cases being designated as involving drug users instead of amphetamine users.

Toxicologic findings

Toxicologic examinations of various degrees of completeness were carried out in 21 of the 43 cases described in the literature, and in 24 of the 26 Ontario coroner's cases. A wide range of drug concentrations was found in any given tissue or in the blood. In the series of cases reported in the literature the blood values ranged from 0 to 4.0 mg/dl, and in the Ontario coroner's series, from 0.002 to 0.70 mg/dl. However, this does not necessarily reflect an extremely wide variation in lethal dose. The times between last intake of drug and the performance of the analysis were widely different and in many cases unknown. It is therefore probable that quite different amounts of drug had been excreted or metabolized, and to this factor must be added the wide range of doses taken. Unfortunately, there is also no consistent pattern of sampling of tissues and body fluids in the different cases. Nevertheless, of those cases for which numerical values for the blood concentration were given, all but two in each group exceeded the value of 0.01 mg/dl, which, according to the Centre of Forensic Science (Toronto), would be expected with a therapeutic dose of amphetamine. This tends not only to confirm the connection of amphetamine with the fatalities, but also to emphasize that most of the decedents had taken high doses.

Epidemiologic inferences

The data that have been presented are too limited and unsystematic to permit any firm conclusions. Nevertheless, the comparison of the findings reported in the literature with the coroner's data provides some valuable clues from which we may infer that mortality in amphetamine users is neither as high as was believed a few years ago ("speed kills"), nor as low as is now frequently claimed.

First, because medical case reporting tends to be qualitative rather than quantitative — recognition of a new phenomenon is usually followed by a cluster of case reports confirming it, but once it has become a part of medical knowledge, publication of reports ceases — the number of

published reports provides no valid estimate of the actual incidence of the conditions. Interestingly, only one death attributed to phenmetrazine has been reported,[31] and none have been attributed to diethylpropion, despite the pharmacologic similarities and widespread nonmedical use of these drugs in some parts of the world.

This conclusion is fully justified by the comparison between the literature and the coroner's series. Although only 5 amphetamine-related deaths were described in the literature in 1972 and 1973, there were at least 16 during that period in Ontario alone, in addition to 10 others in which amphetamine may have had a role; 17 of these were violent deaths and 2 resulted from viral hepatitis, yet no cases in either category were found in the medical literature. A similar predominance of violence and of complications of intravenous injection as the major causes of death in amphetamine users is found in 1969-71 findings in the final report of the Le Dain Commission in Canada[42] and those of Inghe[43] in Sweden.

Most of the overdose fatalities described in the literature occurred in individuals who were not regular heavy users, but the majority of deaths in the group of regular heavy users were due to complications of intravenous injection. This is compatible with the observation that regular use, either oral[2] or intravenous,[15, 44] may lead to the development of high levels of tolerance, so that death by overdose occurs only after a sudden massive increase in dose. According to the final Le Dain report,[42] during 1972 there were approximately 3000 regular and 4000 occasional users of intravenous methamphetamine in Canada and approximately 353 000 regular and occasional users of oral preparations. At the same time there were about 600 reported poisonings, of which 296 were attributed to speed, 115 to phenmetrazine, 51 to amphetamine, 38 to *d*-amphetamine, 20 to methamphetamine, and the rest unstated. If one assumes that the term "speed" refers to illicit methamphetamine for intravenous use, there would appear to be approximately 50 times as great a chance of poisoning with intravenous as with oral use. This does not really contradict the preceding remarks about tolerance in regular users because there is no way of knowing how many of the poisonings occurred in experimenters as opposed to regular users. Moreover, very few of these poisonings had a fatal outcome.

In contrast, there is clearly a greater risk of death from all other causes in the regular intravenous users. Among the Ontario coroner's cases, 16 of the deaths were in known regular intravenous methamphetamine users but only 3 were in oral users. There is insufficient information concerning the route of administration in the other cases; though intravenous and oral routes are the most common, sniffing or "snorting" is also practised.[45] The best current estimates[42, 46] suggest that the population of regular intravenous users in Ontario in 1972 and 1973 numbered about 1500. Treating the 16 fatalities as though all were in men, and assuming that the frequency distribution of amphetamine users in the age range of 15 to 34 years was the same as in the total male population of the same age range in Ontario, the expected number of deaths among users was calculated on two bases: (a) that the mortality would be the same as that in the same age group in the general population according to the Ontario Vital Statistics for 1971, and (b) that it would be the same as that among treated alcoholics.[47] With respect to the former basis for calculation, the results in Table II show that the observed death rate in the users is at least four times as high as would be predicted on the basis of the death rate in the general population. This difference is highly significant ($P < 0.001$). Although the rate also appears higher than in treated alcoholics, the difference is not significant ($P > 0.05$).

Further, the excess mortality in amphetamine users (i.e. observed death rate minus predicted death rate) is actually underestimated here because of the assumptions that have been made. If the absolute numbers had been large enough to permit separate computations for males and females, the lower death rates in the female general population would have given a lower predicted mortality in the user group. In addition, the age distribution of the fatal cases suggests a disproportionately large representation of the younger age groups (15 to 19 years) among the user population than among the general population. If it had been possible to take this into account accurately, the expected mortality would have been lower also. In addition, 10 of the coroner's cases were excluded from the calculation because of inadequate information, but some of these possibly belonged in the group of regular users.

It is therefore reasonable to conclude that the numbers of amphetamine-related deaths reported, both in the medical literature and in coroner's reports, represent an absolute minimum. In Philadelphia alone, for example, during 1969 there were 37 instances of death associated with the presence of amphetamine and other stimulants in the body as detected by toxicologic analysis.[48]

A relatively high turnover rate within the population of regular intravenous methamphetamine users is now recognized. Many of them give up amphetamines and change to heroin or other drugs after 2 or 3 years.[42, 49, 50]

Table II—Comparison of mortality in regular intravenous amphetamine users and in age-matched groups of general population

Population characteristic	Age group (yr)				Total
	15 - 19	20 - 24	25 - 29	30 - 34	
Ontario male population (and % of total male population)	362 100 (29.5)	334 900 (27.3)	286 700 (23.4)	242 000 (19.7)	1 225 700 (100)
Assumed age distribution of amphetamine users*	886	820	703	591	3 000
Mortality					
Per 1000 Ontario males	1.2	1.5	1.2	1.5	
Expected in amphetamine users, based on Ontario male mortality	1.063	1.230	0.843	0.887	4.023
Per 1000 male alcoholics†	0.0	10.3	2.2	3.6	
Expected in amphetamine users, based on mortality of Ontario alcoholics	0.000	8.446	1.546	2.130	12.122
Observed no. of deaths in amphetamine users	4	4	6	2	16

*It is assumed that amphetamine users have the same age distribution as the Ontario male population.
Estimated number of amphetamine users = 1500; period of observation = 2 years; number of man-years of exposure to the risk of death = 3000.
†Based on the mortality experience of alcoholic patients in inpatient and outpatient facilities of the Addiction Research Foundation.

Consequently, deaths from complications of intravenous use beginning during the amphetamine period may well be recorded eventually as being due to the use of other drugs. Among the Ontario coroner's cases, incidental findings at autopsy included multiple foreign body granulomata in the lungs in five (cases 4, 13, 17, 18 and 24) and hepatic inflammatory lesions in six (cases 4, 13, 17, 18, 19 and 22). If the individuals had not died of other causes, these lesions would probably have contributed to morbidity and premature mortality at a later stage. Further, because many of the fatalities of this type occur after prolonged hospitalization or illness, there may be no toxicologic evidence to tie them to specific drug use. One may wonder, for example, how many intracranial hemorrhages occur as a consequence of an unrecognized necrotizing angiitis, so that the role of drug use goes unrecorded.

A truly valid answer must await the completion of longitudinal studies in groups of known amphetamine users. Such studies are in progress in Sweden[43] and possibly elsewhere. Preliminary results[43, 51] indicated a mortality of 3.6% in a 3-year follow-up of 83 cases of viral hepatitis in stimulant users in Stockholm, compared with 0.1% in a comparable age group of the general population. These cases were selected on the basis of already diagnosed liver disease, so that the mortality would be expected to exceed that of the overall population of stimulant users. Another study[43] showed 5.8% mortality in 2 years among 156 users of central nervous system stimulants on a drug maintenance program, most accounted for, once more, by accidental death and complications of drug use. Such studies are needed for Canadian and American populations if we are ever to determine accurately the situation in North America, rather than form clinical impressions or slogans.

With due allowance for the qualifications that have already been made, it is clear that regular heavy amphetamine use, especially by intravenous injection, is associated with a significantly higher mortality than that for the general population. However, it is not strikingly different from that for alcoholics of the same age, and is comparable to that reported for heroin addicts.[52] The alarm with which the public, the press and certain professionals have reacted to the problems of speed and heroin is in sharp contrast to the relative apathy towards the continuing and vastly larger alcohol problem. There are presently about 300 000 alcoholics in Ontario, of whom about 60 000 are in the same age range as the amphetamine users covered in this study, that is, about 40 times as many. Deaths among these young alcoholics numbered about 480 during the same 2-year period in which the 16 deaths occurred among regular amphetamine users. Moreover, excess mortality among alcoholics begins to rise steeply above the age of 35.[47] Such comparison should help to provide needed perspective for an appropriate social response.

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